Complete Summary

GUIDELINE TITLE

Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections.

BIBLIOGRAPHIC SOURCE(S)

Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003 Dec;112(6 Pt 1):1442-6. [5 references] PubMed

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SCOPE

DISEASE/CONDITION(S)

- Severe lower respiratory tract infections caused by respiratory syncytial virus
- Chronic lung disease (formerly called bronchopulmonary dysplasia)
- Congenital heart disease
- Preterm infants

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice

Infectious Diseases
Pediatrics
Pulmonary Medicine

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians
Respiratory Care Practitioners

GUIDELINE OBJECTIVE(S)

- To provide revised recommendations for administering respiratory syncytial virus (RSV) prophylaxis to infants and children with congenital heart disease, for identifying infants with a history of preterm birth and chronic lung disease who are most likely to benefit from immunoprophylaxis, and for reducing the risk of RSV exposure and infection in high-risk children
- To update clinicians on the appropriate use of respiratory syncytial virus immune globulin intravenous (RSV-IGIV) and palivizumab on the basis of data from 5 clinical trials

TARGET POPULATION

Infants at high-risk for respiratory syncytial virus (RSV) infection

INTERVENTIONS AND PRACTICES CONSIDERED

1. Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV) (a polyclonal hyperimmune globulin prepared from donors selected for having high serum titers of RSV neutralizing antibody)
2. Palivizumab (a humanized murine monoclonal anti-F glycoprotein immunoglobulin G1 antibody with neutralizing and fusion inhibitory activity against RSV)

MAJOR OUTCOMES CONSIDERED

- Hospital admissions
- Number of days of hospitalization
- Respiratory tract disease severity
- Cost associated with immunoprophylaxis intervention

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence grade I: evidence obtained from at least one properly designed, randomized, controlled trial

Evidence grade II-1: evidence obtained from well-designed controlled trials without randomization

Evidence grade II-2: evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

Evidence grade II-3: evidence obtained from multiple time series with or without the intervention, or dramatic results in uncontrolled experiments

Evidence grade III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Several economic analyses of respiratory syncytial virus (RSV) immunoprophylaxis have been published and reviewed. The primary benefit of immunoprophylaxis with either agent is a decrease in the rate of RSV-associated hospitalization. None of the 5 randomized, controlled clinical trials have demonstrated a significant decrease in rate of mortality attributable to RSV infection in infants who receive prophylaxis. Most of the economic analyses fail to demonstrate overall savings in health care dollars because of the high cost if all at-risk children were to receive prophylaxis. Estimates of cost per hospitalization prevented have been inconsistent because of considerable variation in the baseline rate of hospitalization attributable to RSV in different high-risk groups. Other considerations that will influence results include the effect of prophylaxis on outpatient costs and a resolution of the question of whether prevention of RSV infection in infancy decreases wheezing and lower respiratory tract problems later in childhood.

Factors other than degree of prematurity, congenital heart disease (CHD), and chronic lung disease (CLD) that may influence the decision regarding prophylaxis include presence of other underlying conditions that predispose to respiratory complications (e.g., neurologic disease in very low birth weight infants), number of young siblings, child care center attendance, anticipation of cardiac surgery, and distance to and availability of hospital care for severe respiratory illness. For many infants who qualify for the approved indications, risk of hospitalization for serious respiratory illness will be low, and the cost and logistic difficulties associated with prophylaxis may outweigh potential benefits.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

1. Palivizumab or Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV) prophylaxis should be considered for infants and children younger than 2 years of age with chronic lung disease (CLD) who have required medical therapy (supplemental oxygen, bronchodilator, diuretic, or corticosteroid therapy) for CLD within 6 months before the anticipated start of the respiratory syncytial virus (RSV) season. Palivizumab is preferred over RSV-IGIV for most high-risk children because of its ease of administration, safety, and effectiveness. (Evidence grade I)
    - Patients with more severe CLD may benefit from prophylaxis during a second RSV season if they continue to require medical therapy for pulmonary or cardiac dysfunction. Individual patients may benefit from decisions made in consultation with neonatologists, pediatric

intensivists, pulmonologists, or infectious disease specialists. There are limited data regarding the effectiveness of palivizumab during the second year of life, although children with CLD or congenital heart disease (CHD) who require ongoing medical therapy may experience severe RSV infections.

2. Infants born at 32 weeks´ gestation or earlier may benefit from RSV prophylaxis, even if they do not have CLD. For these infants, major risk factors to consider include their gestational age and chronologic age at the start of the RSV season. (Evidence grade I)
    - Infants born at 28 weeks´ gestation or earlier may benefit from prophylaxis during their first RSV season whenever that occurs during the first 12 months of life. Infants born at 29 to 32 weeks´ gestation may benefit most from prophylaxis up to 6 months of age. For the purpose of this recommendation, 32 weeks´ gestation refers to an infant born on or before the 32nd week of gestation (i.e., 32 weeks, 0 days). Once a child qualifies for initiation of prophylaxis at the start of the RSV season, administration should continue throughout the season and not stop at the point an infant reaches either 6 months or 12 months of age.
3. Although palivizumab and RSV-IGIV have been shown to decrease the likelihood of hospitalization for infants born between 32 and 35 weeks of gestation (i.e., between 32 weeks, 1 day and 35 weeks, 0 days) (Evidence grade I), the cost of administering prophylaxis to this large group of infants must be considered carefully.
    - Most experts recommend that prophylaxis be reserved for infants in this group who are at greatest risk of severe infection and who are younger than 6 months at the start of the RSV season. Epidemiologic data suggest that RSV infection is more likely to lead to hospitalization for these infants when the following risk factors are present: child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease. However, no single risk factor causes a very large increase in the rate of hospitalization, and the risk is additive as the number of risk factors for an individual infant increases. Therefore, prophylaxis should be considered for infants between 32 and 35 weeks´ gestation only if 2 or more of these risk factors are present.
    - Exposure to tobacco smoke is a risk factor that can be controlled by the family of an infant at increased risk of RSV disease, and tobacco smoke control measures will be far less costly than palivizumab prophylaxis. High-risk infants never should be exposed to tobacco smoke. High-risk infants should be kept away from crowds and from situations where exposure to infected individuals cannot be controlled.
    - Participation in child care should be restricted during the RSV season for high-risk infants whenever feasible. Parents should be instructed on the importance of careful hand hygiene.
    - All high-risk infants and their contacts should be immunized against influenza beginning at 6 months of age.
4. Prophylaxis against RSV should be initiated just before the onset of the RSV season and terminated at the end of the RSV season. In most seasons and in most regions of the Northern Hemisphere, the first dose of palivizumab should be administered at the beginning of November and the last dose should be administered at the beginning of March, which will provide protection into April. (Evidence grade III)

- To understand the epidemiology of RSV in their area, physicians should consult with local health departments or diagnostic virology laboratories or the Centers for Disease Control and Prevention if such information is not available locally. Decisions about the specific duration of prophylaxis should be individualized according to the duration of the RSV season. Pediatricians may wish to use RSV hospitalization data from their own region to assist in the decision-making process.

5. Children who are 24 months of age or younger with hemodynamically significant cyanotic and acyanotic CHD will benefit from 5 monthly intramuscular injections of palivizumab (15 mg/kg). (Evidence grade I)
    - Decisions regarding prophylaxis with palivizumab in children with CHD should be made on the basis of the degree of physiologic cardiovascular compromise. Infants younger than 12 months with CHD who are most likely to benefit from immunoprophylaxis include:
        a. Infants who are receiving medication to control congestive heart failure (CHF)
        b. Infants with moderate to severe pulmonary hypertension
        c. Infants with cyanotic heart disease
    - Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab (15 mg/kg) should be considered as soon as the patient is medically stable.

    The following groups of infants are not at increased risk from RSV and generally should not receive immunoprophylaxis:

    - Infants and children with hemodynamically insignificant heart disease (e.g., secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus)
    - Infants with lesions adequately corrected by surgery unless they continue to require medication for congestive heart failure
    - Infants with mild cardiomyopathy who are not receiving medical therapy

    Dates for initiation and termination of prophylaxis should be based on the same considerations as for high-risk preterm infants. Unlike palivizumab, RSV-IGIV is contraindicated in children with cyanotic CHD.

6. Palivizumab or RSV-IGIV prophylaxis has not been evaluated in randomized trials in immunocompromised children. Although specific recommendations for immunocompromised patients cannot be made, children with severe immunodeficiencies (e.g., severe combined immunodeficiency or severe acquired immunodeficiency syndrome) may benefit from prophylaxis. If these infants and children are receiving standard IGIV monthly, physicians may consider substitution of RSV-IGIV during the RSV season. (Evidence grade III)
7. Because RSV-IGIV and palivizumab are not effective in the treatment of RSV disease, neither is licensed for this indication. (Evidence grade I)

8. Limited studies suggest that some patients with cystic fibrosis may be at increased risk of RSV infection. However, there are insufficient data to determine the effectiveness of palivizumab use in this patient population.
9. If an infant or child who is receiving immunoprophylaxis experiences a breakthrough RSV infection, prophylaxis should continue through the RSV season. (Evidence grade III)
    - This recommendation is based on the observation that high-risk infants may be hospitalized more than once in the same season with RSV lower respiratory tract disease and the fact that more than one RSV strain often co-circulates in a community.
10. Physicians should arrange for drug administration within 6 hours after opening a vial, because this product does not contain a preservative.
11. Recommendations cannot be made regarding the use of palivizumab as a means of prevention of nosocomial RSV disease.
    - RSV is known to be transmitted in the hospital setting and to cause serious disease in high-risk infants. In high-risk hospitalized infants, the major means to prevent RSV disease is strict observance of infection control practices, including the use of rapid means to identify and isolate RSV-infected infants. If an RSV outbreak is documented in a high-risk unit (e.g., pediatric intensive care unit [ICU]), primary emphasis should be placed on proper infection control practices, especially hand hygiene.

12. Palivizumab does not interfere with the response to vaccines. Infants and children receiving prophylaxis with RSV-IGIV should have immunization with measles-mumps-rubella and varicella vaccines deferred for 9 months after the last dose of RSV-IGIV.
    - The use of RSV-IGIV should not alter primary immunization schedule for other recommended immunizations. Available data at this time do not support the need for supplemental doses of any of these routinely administered vaccines.

Definitions:

Evidence Grading

Evidence grade I: evidence obtained from at least one properly designed, randomized, controlled trial

Evidence grade II-1: evidence obtained from well-designed controlled trials without randomization

Evidence grade II-2: evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

Evidence grade II-3: evidence obtained from multiple time series with or without the intervention, or dramatic results in uncontrolled experiments

Evidence grade III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Benefits

Prevention of severe lower respiratory tract infections caused by respiratory syncytial virus (RSV) in high-risk infants, children younger than 24 months with chronic lung disease (formerly called bronchopulmonary dysplasia), and certain preterm infants

Specific Benefits

Palivizumab is preferred for most high-risk infants and children because of ease of intramuscular administration. Monthly administration of palivizumab during the RSV season results in a 45 to 55% decrease in the rate of hospitalization attributable to RSV.

POTENTIAL HARMS

Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV)

- Volume overload
- Interference with the immune response to some live-virus vaccines; therefore, immunization with measles-mumps-rubella and varicella vaccines should be deferred for 9 months after the last dose. The manufacturer has suggested an additional dose of vaccine to ensure adequate immune response to diphtheria and tetanus toxoids and acellular pertussis, H influenzae type b, and oral poliovirus vaccines; however, available data do not support the need for supplemental doses of routinely administered vaccines.
- Mild decrease in oxygen saturation and fever

Palivizumab

Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab should be considered as soon as the patient is medically stable.

CONTRAINDICATIONS

CONTRAINDICATIONS

Respiratory syncytial virus immune globulin intravenous (RSV-IGIV) is contraindicated in children with cyanotic congenital heart disease (CHD)

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003 Dec;112(6 Pt 1):1442-6. [5 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Dec

GUIDELINE DEVELOPER(S)

American Academy of Pediatrics - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Pediatrics

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Committee on Fetus and Newborn, 2003-2004

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

American Academy of Pediatrics (AAP) Policies are reviewed every 3 years by the authoring body, at which time a recommendation is made that the policy be retired, revised, or reaffirmed without change. Until the Board of Directors approves a revision or reaffirmation, or retires a statement, the current policy remains in effect.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Academy of Pediatrics (AAP) Policy Web site.

Print copies: Available from American Academy of Pediatrics, 141 Northwest Point Blvd., P.O. Box 927, Elk Grove Village, IL 60009-0927.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Meissner HC, Long SS, and the Committee on Infectious Diseases and the Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Technical report. Pediatrics 2003 Dec;112(6 Pt 1):1447-52.

Electronic copies: Available from the American Academy of Pediatrics (AAP) Web site.

Print copies: Available from American Academy of Pediatrics, 141 Northwest Point Blvd., P.O. Box 927, Elk Grove Village, IL 60009-0927.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 20, 2004. The information was verified by the guideline developer on June 23, 2004.

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